REMARKS

The Office Action and cited and applied reference have been carefully reviewed. Claims 7-9 are allowed. Claims 1-9, 11, and 14-17 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 3-6 and 11 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that applicants' argument is not persuasive because it is noted that the term "substantially" in the examples presented by applicants is used to describe the degree of a physical feature ("substantially flat"), or the level of an activity (U.S. patent no. 5,429,936, claim 11). On the other hand, the examiner states that the term "substantially" in the instant claims is used to describe an amino acid sequence. This rejection is obviated by the amendment to claims 3 and 11 to make clear that it is the physicochemical property of the interferon-γ production inducing activity by immunocompetent cells that is "not substantially altered".

Claims 3-6 remain rejected under 35 U.S.C. 112, first paragraph. The Examiner states that the specification does not reasonably provide enablement for claims to variants as defined in claim 3. The examiner further states that the

main issue is not whether a skilled artisan is able to generate and test the variants of SEQ ID NO:2 with the claimed physicochemical properties; rather, the issue is that the claim limitation in part (4) of claim 3 that "wherein said variant has the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID NO:2 replaced..." reads on a functional equivalent of IGIF with the cited physicochemical properties which may not be a sequence variant of SEQ ID NO:2 as there is no upper limit in the claim as to how many amino acid residues may be replaced. This rejection is respectfully traversed.

Applicants have now amended claim 3 to make it clear that the variant is one which is a sequence variant of SEQ ID NO:2. It is believed that such a variant as defined in the amended claim 3 would have been reasonably obtained by one of skill in the art once the amino acid sequence of SEQ ID NO:2 is given, taking into account the state of the art at the time the present invention was made.

Applicants also believe that a skilled artisan would understand the upper limit of the number of amino acid residues which may be replaced in the variant, even if there is no explicit limitation recited in claim 3. The upper limit is considered to be several to dozens of amino acid residues at most. As the examiner indicated in the Office Action, the

specification does not provide explicit recitation about the upper limit. However, it is believed that the upper limit would have been obvious to one of skill in the art in view of the state of the art because it would have been routine for one of skill in the art at the time the present invention was made to obtain a variant having substantially the same activity as an original protein by altering a part of a given amino acid sequence of the protein. A skilled artisan had tried to obtain a variant having substantially the same activity as an original protein before the present application was filed and easily succeeded in obtaining such variants. Furthermore, the applicants believe that amended claim 3 should be allowed because if claim 3 is rejected, the variants of SEQ ID NO:2 would not be protected allowing a third party to freely utilize the present invention, which would be unfair.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 2, 11, 14 and 15 remain rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for claims limited in scope to a protein with SEQ ID NO:2, wherein residue 70 is methionine or threonine, does not reasonably provide enablement for variants with

properties listed in these claims. This rejection is respectfully traversed.

The recitation of the physicochemical property of "(4) Partial amino acid sequence" has been deleted from claims 1 and 2. Since the reference to variants has been deleted, applicants consider that the issue of enablement for the variants is now moot. Applicants believe that the claimed IFN-γ production inducing agent and pharmaceutical composition are well defined with the term "IGIF" and "IL-18", which are well known to a person skilled in the art, as well as its physicochemical properties, such as (1) Molecular weight, (2) Isoelectric point, and (3) Biological activity. Applicants have also amended claim 11 in which a purified interferon-gamma production inducing protein is defined with the term "IGIF" and "IL-18"; its physicochemical properties, such as (1) Molecular weight, (2) Isoelectric point, (3) Biological activity and (4) Partial amino acid sequence; and its function that it reacts with a monoclonal antibody specific to an interferon-gamma production inducing protein having the amino acid sequence of SEQ ID NO:2 or a sequence variant of the protein having one or more of the same antigenic fragments as in the amino acid sequence of SEQ ID NO:2. Applicants believe that the amendments to the claims overcome this rejection.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-6, 11, 14, and 15 remain further rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons set forth in the last Office Action, paper no. 7, at pages 7-8. This rejection is respectfully traversed.

Applicants would like to draw the examiner's attention to the disclosure in the specification at page 16, first paragraph, and from page 19, second paragraph to page 21, first paragraph. Applicants believe that the following subject matter are well described in the present specification:

> "the functional variants which have the amino acid sequence of SEQ ID NO:2, and react with a monoclonal antibody specifically reacting with SEQ ID NO:2"

and

> "the functional variants which have a sequence variant of SEQ ID NO:2 with one or more of the same antigenic fragments as in the amino acid sequence of SEQ ID NO:2, and react with a monoclonal antibody specifically reacting with said sequence variant".

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-3, 5, 6, 11, 14 and 15 remain rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al. (1993) for the reasons set forth in the previous Office Actions, paper no. 4 at page 7, and paper no. 7 at pages 9-10.

The examiner considers that the claimed protein and Nakamura's factor are the same substance, relying on Okamura et al. (Infect. Immun. 63 3966-3972, 1995), which was published after the present application was filed and after Nakamura was published. This rejection is respectfully traversed.

The molecular weight of Nakamura's factor, measured with the same method as the present invention, is 50,000 - 55,000 (50-55 kDa) as recited in Nakamura, page 66, right column and page 67, left column, Figure 2. Although Okamura states that Nakamura's factor produces a protein having a molecular weight of 19 kDa when treated on 0.1% SDS-PAGE in the presence of DTT, and that the protein is IGIF, this cannot allow one of skill in the art to conclude that the presently claimed protein and Nakamura's factor are the same substance because of the following reasons:

First, Okamura recites as follows at page 3969, in the middle of the left column,

> Thus, IGIF in the serum sample was proved to be the same IGIF as that found in the liver extract, and it was considered to be bound to another protein or to exist in an oligomeric form. (emphasis is added by the applicants)

According to the disclosure cited above, it is clear that Okamura considers Nakamura's factor to be a substance which exists in a state where IGIF and another protein are bound together (i.e., Nakamura's factor is not a homogeneous protein). It cannot be construed that Okamura concludes that Nakamura's factor is same as IGIF.

Furthermore, applicants submit that the presently claimed protein having a molecular weight of 19,000 ± 5,000 can be distinguished from Nakamura's factor in its existing form, even if Nakamura's factor is an oligomeric protein or an oligomer of IGIF. Attached hereto is a copy of relevant pages of the "Concise Encyclopedia Biochemistry", second edition, p. 570, 1988, to explain the existing form of proteins. It should be noted that it is well known to a those of skill in the art that physicochemical properties of protein may differ depending on its existing form, i.e., monomer or oligomer. In view of this well-known fact, applicants submit that Nakamura's factor is distinguishable from the claimed protein in its existing form, i.e., oligomer or monomer, even if Nakamura's factor comprises IGIF.

Second, it should be noted that Nakamura's factor is a substance which loses IFN-γ inducing activity when treated on SDS-PAGE, whereas the claimed protein retains IFN-γ inducing activity even after treatment on SDS-PAGE. The examiner, however, states that it is not understood from the specification that the claimed protein retains IFN-γ inducing activity even after treatment on SDS-PAGE.

The examiner's attention is invited to the specification at page 23, Experiment 2-1, which reads as follows;

> the purified protein prepared by the method in Experiment 1 was electrophoresed in a sodium dodecyl sulfate (SDS) polyacrylamide gel free of reducing agent to mainly show a single protein band with an IFN-γ inducing activity at a position corresponding to about 19,000 + 5,000 daltons. (emphasis added by the applicants)

As clearly stated in that part of the specification, the claimed protein retains INF-γ inducing activity even after treatment on SDS-PAGE. This is also positively recited in new claim 16. If the claimed protein did not retain its IFN-γ inducing activity even after treatment on SDS-PAGE, then it would have been impossible to determine the molecular weight of the claimed protein to be "about 19,000 ± 5,000 daltons" in Experiment 2-1, because a molecular weight measured on a protein which has lost its activity on SDS-PAGE treatment does

not reflect the true molecular weight which the protein having it activity inherently possesses. This is commonly recognized in the art. In fact, Nakamura states at page 68, right column, lines 9-11,

> Since the factor lost its activity in SDS-PAGE, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor.

This statement in Nakamura proves that the applicants' above arguments are correct.

Nakamura does not make obvious the presently claimed invention. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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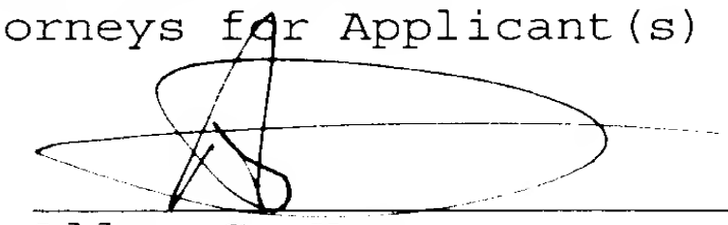
By 
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